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Bioheat Transfer Basis of Human Thermoregulation: Principles and Applications

Thermoregulation is a process that is essential to the maintenance of life for all warm-blooded mammalian and avian species. It sustains a constant core body temperature in the face of a wide array of environmental thermal conditions and intensity of physical activities that generate internal heat. A primary component of thermoregulatory function is the movement of heat between the body core and the surface via the circulation of blood. The peripheral vasculature acts as a forced convection heat exchanger between blood and local peripheral tissues throughout the body enabling heat to be convected to the skin surface where is may be transferred to and from the environment via conduction, convection, radiation, and/or evaporation of water as local conditions dictate. Humans have evolved a particular vascular structure in glabrous (hairless) skin that is especially well suited for heat exchange. These vessels are called arteriovenous anastomoses (AVAs) and can vasodilate to large diameters and accommodate high flow rates. We report herein a new technology based on a physiological principle that enables simple and safe access to the thermoregulatory control system to allow manipulation of thermoregulatory function. The technology operates by applying a small amount of heating local to control tissue on the body surface overlying the cerebral spine that upregulates AVA perfusion. Under this action, heat exchangers can be applied to glabrous skin, preferably on the palms and soles, to alter the temperature of elevated blood flow prior to its return to the core. Therapeutic and prophylactic applications are discussed.
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Background of Bioheat Transfer in Thermoregulation Research

Human thermoregulation has been a subject of intense and broad-based investigation for well over a century. This work has been largely in the hands of researchers in physiology and medicine, with engineers contributing primarily to developing an understanding of the system control and mechanistic functions. The target of thermoregulation is to control the body's core temperature to remain constantly within a thermoneutral zone in the face of a wide range of potential internal and external loading conditions. The mechanisms of thermoregulation comprise a complex and highly nonlinear control system. Much has been learned about thermoregulation and how it works, and recently a comprehensive two-volume state-of-the-art review of the field of thermoregulation edited by Romanovsky was published [1,2], followed by informative summaries of the review [3,4].

Developing a robust working understanding of thermoregulatory function has deservedly occupied the attention of a wide range of scientific and medical disciplines. Werner has notably described with great insight the diversity of intellectual expertise required to grasp and apply the many features of thermoregulatory processes in his review of the first Handbook volume [3]. It is quoted as follows.

"The analysis of thermoregulatory processes needs:

- unifying insights from physics and chemistry, from biology and physiology, from system theory and control engineering, from environmental and occupational medicine, from pharmacology and neurology, from anesthesiology and intensive care, and many other clinical disciplines;
- unifying approaches to understand whole-body systems and the interaction of thermoregulation with the cardiovascular and the respiratory system, with metabolism, and with body fluid and osmoregulation;
- unifying scientific attempts on different levels of analysis: on the molecular, on the neural, on the energetic, and on the informational (system) level." [3]

Unfortunately, there is no mention of heat transfer engineering on this rather inclusive list of disciplines, which is interesting given that all of the key processes that enable thermoregulation involve heat transfer either internally or externally to the body. Some particular roles played by heat transfer in thermoregulation are the topic of this paper.

Heat Transfer in Thermoregulation. Heat transfer processes endogenous to thermoregulation occur via all available modes: conduction, convection, radiation, phase change, and internal generation. Much thermoregulatory function transpires in the absence of overt awareness by most persons except when it enters into extreme modes such as intense shivering and sweating. Such situations often lead to behavioral modifications including adjusting clothing ensemble, moving into or out direct sunlight, or drinking a hot or cold beverage. Nonetheless, these often-subtle thermal processes are integral to the maintenance of health and comfort. In this paper, we will consider these processes both individually and collectively and how they unfold in exquisite coordination to effectively modulate the body's temperature under an exceptional array of physiological, metabolic, and environmental challenges. Plus, we will introduce some of our discoveries on how to intervene and manipulate control of these processes to medical and personal comfort benefit.

Objective: To Maintain a Stable Body Core Temperature. Coordination of the various modes and intensities of heat transfer requires a remarkably complex control system that has long been

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studied in depth, but that has defied consensus of understanding [5,6]. Indeed, such basic control system concepts as the existence of a thermostat having a set point value to serve as a comparator reference to drive compensatory mechanisms are often denied [7]. Rather, considerable evidence supports the mechanism of thermoregulatory control occurring via a multisensor, multiprocessor, multi-effector proportional feedback system, all of which are integrated into physiological function in an elegantly effective manner [8,9]. Given that the objective of thermoregulatory function is to keep the body core temperature (T_{core}) within a narrow range that is essential for the regulation of many other dependent processes within the body, the entire ensemble of contributing activities can be simply viewed in terms of the first law of thermodynamics (written from the perspective of a macroscopic system state defined in terms of T_{core}). All of the multitude of heat flows, afferent inputs and efferent outputs serve the purpose of defending the thermal state of the body against deviations from a thermal neutral zone as defined in terms of a heavy weighting for T_{core} and a lighter weighting for skin and other peripheral tissue temperatures.

Conservation of Energy as a Governing Principle. Our starting point for analysis of thermoregulatory function in humans is to apply the conservation of energy since the two perspectives are intrinsically linked [10]. The system of interest is the human body, with particular attention directed to a subsystem consisting of the core for which the thermal state is described by T_{core}. Although T_{core} is single property value used to identify the thermal state, in actuality the various tissues and organs that comprise the core are not isothermal, since there will be inherent temperature differentials among organs that may have greatly differing perfusion and metabolic rates at rest (brain and liver are higher and heart and kidney are lower) and compared with blood and the tissues through which it is perfused. However, from a macroscopic perspective, the visceral organs and tissues plus the brain can be integrated together as having a core thermal energy storage potential given by T_{core}. This temperature is distinguished from the temperatures in more peripheral regions of the body located distal to the core, such as the limbs, where the integrated temperature can be classified as T_{distal}, in the regions at the proximity of the body surface, where the integrated temperature can be classified as T_{skin}, and in the environment surrounding the body with which it may interact via heat transfer, where the integrated temperature can be classified as T_{envir}.

Conservation of energy may be written macroscopically for the body as a whole system. Figure 1 shows the body as defined in terms of multiple subsystems that may interact with each other, and each of which may have a conservation of energy equation written. The most relevant subsystem for thermoregulation is the body core. Each term in the conservation of energy equation will have a relevant constitutive expression for its operation which, when implemented, produces a governing partial differential equation that may be applied to describe the behavior of the system under defined initial and boundary conditions [11].

The conservation equation states that the time rate of change of the conserved property (energy stored in the system) is equal to the rates of all of mechanisms of energy additions and removals across the system boundary, plus internal generation. The relevant system and interactions with the environment and among multiple subsystems are shown in Fig. 1. The conservation of energy is written for the body as a complete system, as given in the following equation:

$$\frac{d(\text{energy stored in body})}{dt} = \sum \text{rates of energy additions} - \sum \text{rates of energy losses} \quad (1)$$

Constitutive Expressions for the Conservation Equation. Each term in the conservation of energy equation has a dedicated

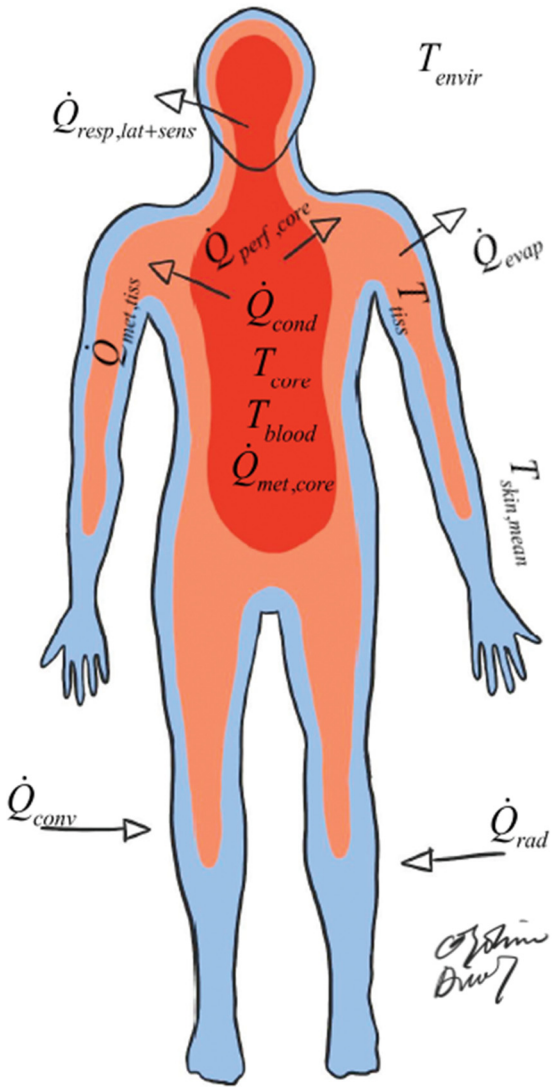


Fig. 1 Human thermoregulatory system with subsystems for core, distal tissue, and skin. Internal energy interactions include energy generation, convection associated flow of blood between different subsystems, and conduction driven by internal temperature gradients. External energy interactions include convection and radiation with the environment, latent and sensible energy flows associated with respiration, and evaporation of water from the body surface via sweating and transpiration.

constitutive expression. For thermoregulation processes, the relevant constitutive terms for Eq. (1) are as follows:

$$\frac{d(\text{energy stored in body})}{dt} = m_{body} c_{body} \frac{dT_{body}}{dt} \quad (2)$$

For the additions and loses, Fig. 1 shows arbitrary positive directions for the various energy transfers. If, in fact, the actual directions were different, the signs would be reversed, i.e., additions would count as losses, and vice versa

$$\sum \text{rates of energy additions} = \dot{Q}_{met} + \dot{Q}_{conv} + \dot{Q}_{rad} \quad (3)$$

$$\sum \text{rates of energy losses} = \dot{Q}_{evap} + \dot{Q}_{resp,lat+sens} \quad (4)$$

It is particularly advantageous for understanding thermoregulation to write the conservation of energy equation for the body core subsystem. Based on the definitions presented in Fig. 1 and the

assumed positive directions for individual heat flows, this expression is

$$\frac{d(\text{energy stored in core})}{dt} = m_{\text{core}} c \frac{dT_{\text{core}}}{dt} = \dot{Q}_{\text{met,core}} - \dot{Q}_{\text{perf,core}} - \dot{Q}_{\text{cond}} \quad (5)$$

There are one or more specific constitutive expressions available for each term on the right sides of Eqs. (3)–(5). These terms have been explored in great depth for many years as they have direct relevance to human energy interactions with the environment. On the one hand, the conduction, convection, and radiation equations may be developed from heat transfer first principles. Alternatively, experiments have been conducted variously over the past century to measure thermal interactions between humans and their environments under many types and levels of stress, with the results expressed via empirical relations for calculating energy exchanges [12]. For example, Colin and Houdas [13] measured convection from the body surface over a matrix of ambient air temperatures and flow velocities and fit an empirical equation to the data to obtain the relationship

$$\dot{Q}_{\text{conv}} = (2.3 + 7.5V^{0.67})(T_{\text{skin,mean}} - T_{\text{envir}}) \quad (6)$$

where the units of $\dot{Q}_{\text{conv}}$ are kcal/m^2 h, air velocity V are m/s, and T are °C. Note that Eq. (6) is written in a format that yields a positive convective heat flux when the skin temperature exceeds the air temperature, consistent with the assumed flow direction shown in Fig. 1. As is typical for convective heat transfer analysis, other researchers have conducted complementary experiments and fit equations with similar formats to their data, but using different combinations of coefficients and exponents. Also, the coefficients and exponents are adjusted for physiological and environmental factors such as forced and free convection flows, prone, seated and standing profiles relative to the fluid velocity vector, fluid composition (primarily air and water), and thermodynamic state (T, p, relative humidity). The empirical expressions for the other energy interactions have a similar flavor.

Convective Heat Transfer by Blood Perfusion—Macroscopic Scale. A term of particular interest in Eq. (5) is $\dot{Q}_{\text{perf,core}}$, which refers to the convective transport of blood between the core and peripheral tissue where heat may be exchanged with the environment. It is written with a negative sign in Eq. (5) because the body core temperature is often warmer than the environment resulting in a heat loss, but under some important circumstances such as thermally driven therapies, the heat flow direction is reversed. The perfusion term measures the difference in the enthalpy of blood flowing between the body core and the skin as heat is shuttled between these two regions. The constitutive expression for this term is

$$\dot{Q}_{\text{perf,core}} = \dot{m}_b c_b (T_{\text{core}} - T_{\text{skin}}) \quad (7)$$

where $\dot{m}_b$ is the rate of blood flow from the core to the skin in kg/s, c_b is the specific heat of blood in J/kg K, and T_{core} and T_{skin} are the averaged temperatures of the core and skin, respectively, in K. An inherent assumption embedded in Eq. (7) is that there is negligible heat exchange between blood and surrounding tissues as it flows convectively between the core and skin. This assumption has been proven correct based on robust analysis by Chato of forced convection heat transfer throughout the vascular network [14]. Chato showed that there is significant heat exchange between blood and perfused tissue only when the vessels branch to the size of arterioles and smaller. Thus, the vasculature can function effectively as a conduit for convective heat flow between the core and skin.

Convective Heat Transfer by Blood Perfusion—Microscopic Scale. A different expression for perfusion is encountered frequently in bioheat transfer as shown in the following equation:

$$\dot{Q}_{\text{perf,tiss}} = (\rho c)_b \omega_b (T_{\text{blood}} - T_{\text{tiss}}) \quad (8)$$

where ρc refers to the density and specific heat of blood in units of kg/m^3 and J/kg K, respectively, ω_b to the perfusion rate in ml blood flow through ml local tissue in units of 1/s, T_{blood} is the temperature of blood entering a local region of tissue, and T_{tiss} is the temperature of that tissue. This term describes the convective exchange of heat between blood and tissue through which it is being perfused. It occurs in the conservation of energy equation, often referred to as the Pennes equation [15], written for a small local tissue system, as follows:

$$\rho c \frac{\partial T_{\text{tiss}}}{\partial t} = \nabla \cdot k \nabla T_{\text{tiss}} + (\rho c)_b \omega_b (T_{\text{blood}} - T_{\text{tiss}}) + \dot{Q}_{\text{met,tiss}} \quad (9)$$

This equation applies for blood perfused tissue in the core, in the skin, in tissue distal from the core such as muscle, and in specific visceral organs. Alternate more complex models have been proposed to include the effects on convection of specific vascular geometry and architecture that may vary greatly throughout the body [16,17]. The outcome is that as blood flows in the peripheral microscopic circulatory elements, a local thermal equilibrium is achieved between the blood and tissue.

Heat Transfer Based Mathematical Models of Thermoregulatory Function. It has long been desirable to be able to predict the operation of the various heat flows involved in thermoregulation in modulating body energy storage (and temperature) in response to a diverse array of environment stresses, types and intensities of physical activity and physiological behavior according to circadian rhythm, distinct illnesses, and trauma experiences. To this end, mathematical models of thermoregulatory processes have been postulated over the past half century plus [18–21]. From the beginning, the complexity of the anatomical and physiological control aspects of the system necessitated simulation with the aid of a computer. Earlier studies were conducted with analogue computers with simplified representations of the human body in three [21] or four [20] elements arranged concentrically from the core to the surface, connected with a common blood circulatory system and governed by a central set point controller. Necessary components of these models include constitutive relations for each individual heat transfer and energy storage effector mechanism, and an overall energy balance for the central body system being regulated, and a control algorithm to represent the coordination and modulation among all the various processes that comprise the active regulator. In the same time frame, early scientific computers were adopted for thermoregulatory studies [22,23]. Our engineering colleague Gene Wissler at the University of Texas spent more than 50 years building and refining an advanced model of thermoregulation that has been proven for many different environmental stressors [18]. His considerable effort is summarized in a recent text that was published posthumously [24].

Over the ensuing decades, the capabilities of mathematical models for thermoregulation have increased dramatically as the number and accuracy of anatomical elements have grown along with the sophistication of control algorithms. For example, the Wissler thermoregulation model has now evolved to embody 6300 computational nodes [18]. One of the greatest challenges to building a mathematical model to simulate thermoregulatory behavior is to accurately describe the control function for coordination among the multitude of parallel effector mechanisms in activation and dose, as described by Romanovsky in his comprehensive review [9].

One major advance in mathematical models in recent years has been the inclusion of glabrous skin blood flow (GSBF) which can have a major effect on the convection of heat from the core to the skin and then further to the environment [25–29]. The dominate vascular element in glabrous skin is the arteriovenous anastomoses (AVAs) that may vasodilate to diameters an order of

magnitude larger than capillaries, providing a low resistance pathway that can accommodate high blood flow rates and enhanced convective heat transfer.

The unique vascular morphology of the AVAs that contributes to their efficacy in convective heat transfer between blood and tissue has previously been discussed by our research team [30]. This morphology is illustrated in Fig. 2 showing micrographs of dermal casts from the palmar and dorsal aspects of human fingers. It is quite apparent that the AVAs provide an enhanced capability for convective heat transfer between perfused blood and the embedding interstitial tissue.

The AVAs play a major role in thermoregulation. Nonetheless, there are still very few models of thermoregulation that include the explicit influence of perfusion to the AVAs [18,31,32]. A difficult conceptual hurdle is how to effectively build control of AVA blood flow during thermoregulation into a computer model. There are clearly remaining opportunities for further contributions in this arena, which is one of the objectives of the current research project.

Control of Thermoregulatory Processes. The mechanism of control exerted over the thermoregulatory process is complex and has been actively debated for a very long time as researchers have sought to understand how the human body can maintain a remarkably constant core temperature in the face a multitude of external and internal stressor inputs [33]. Plus, thermoregulation has multiple parallel effector mechanisms of differing intensity and anatomical implementation sites.

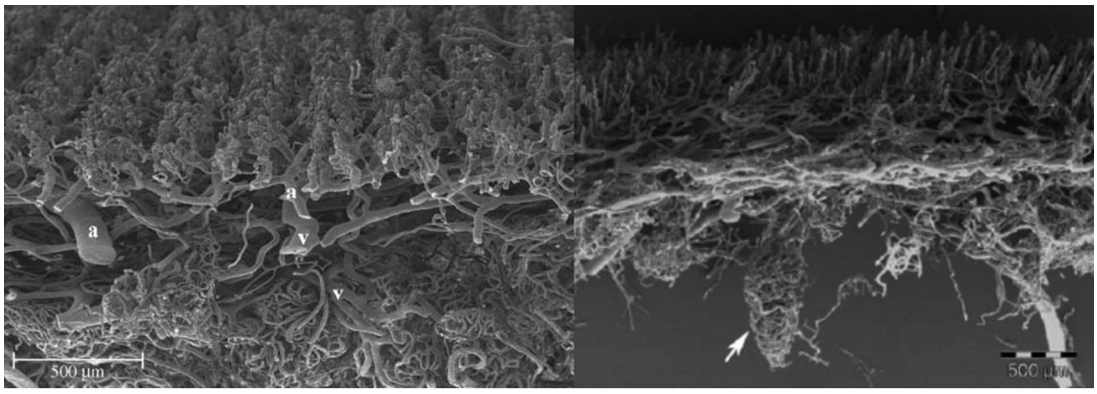
Control Schema for Thermoregulation. Early concepts assumed that there was a single operative control center and feedback loop to regulate body temperature. Thermoregulation was viewed as akin to a simple heating ventilating airconditioning (HVAC) system in which a set point temperature for a critical internal system volume was defined with the effector actuators responding as deviations developed between the set point and monitored temperatures. Differing actuators (such as vasoconstriction and vasodilation, shivering, and sweating) would be activated selectively as a function of the nature of the input signals from thermosensors in the body. However, as a more complete understanding of the mechanisms of thermoregulation has emerged, it has become compellingly clear that this is not the case [34–37]. Rather, it is recognized that thermoregulation can occur as a balance between controlling and controlled processes [8] to produce heat flows leading to core temperature stability. Control signals are generated by temperatures derived from central locations deep in the body and peripheral locations toward the surface, especially the skin. The body incorporates a huge number of microscopic thermal sensors with outputs processed independently via dedicated effector circuits whose integrated function results in tight control over body temperature [9,38,39].

Circadian Factors in Regulation of Core Temperature. Although the human thermoregulation system holds the core body temperature to within a tight tolerance, by no means does this temperature remain continuously constant. In fact, there is a programed, significant cyclic variation on the order of 1 °C over the 24-h period of each day that far exceeds the control tolerance of thermoregulation [34,40–42]. Of course, it is well known that the circadian cycle has a much broader physiological impact than just thermoregulation, effecting sleep, metabolism, immunity, physical performance capability, behavioral function, and the list goes on and on [43,44]. It is interesting that the thermoregulation circadian rhythm has a leading effect in directing many of the other circadian-oriented phenomena, including sleep [45–48].

The central circadian pacemaker that controls core body temperature is the suprachiasmatic nuclei of the hypothalamus, as well as by peripheral clocks that differentially modulate the intensity of thermogenic metabolic processes [49,50]. The suprachiasmatic nuclei coordinate daily cyclic activities of physiology and behavior in synchrony with solar time. This timing function is conveyed to every cell in the body to produce a remarkably coordinated control touching nearly all physiological functions. It is in this context that thermoregulation is coordinated with other key functions such as sleep. Driving bioheat transfer processes is an important component of this coordination.

The circadian cycling of body temperature consists of warming during the daytime and cooling overnight. In order for the core body temperature to drop at the time of sleep onset, it is necessary that there be a heat diversion to the environment, as described in Eq. (1). This process is facilitated by convective transport from the core to the body surface by the circulation of blood. In particular, when the AVAs become vasodilated, they can accommodate a large net blood flow from the core where the temperature is nearly always higher than the environment, in effect causing convective cooling of the blood before it returns to the core where it acts to lower the temperature. Profuse perfusion through the AVAs results in a sensation of warm hands and feet, which is a condition known for effective induction of sleep onset [51].

Thus, it is well known that the thermal circadian cycle leads the sleep cycle [52]. A very important collateral benefit of AVA



(*a*) (*b*)

Fig. 2 Vascular casts taken from (*a*) palmar (glabrous) and (*b*) dorsal (nonglabrous) aspects of the human finger. The surface of the dermis is oriented upward. The superficial plexus of fine capillary riser loops is in the upper portion of the casts. The space for AVAs is at the bottom. The glabrous skin shows a tight tangle of AVAs, although they were not fully dilated when the cast was made. At maximum vasodilation, an AVA can exceed the diameter of a capillary by 10× or more. The nonglabrous skin has no AVAs and only a single hair follicle (denoted by arrow). Larger arteriolar and venular elements broken from the casts are denoted by a and v, respectively. Adapted from Ref. [30].

vasodilation in conjunction with preparing for sleep onset is the fact that the enlarged diameters of the AVAs, which can exceed by an order of magnitude the caliber of the capillaries that present the alternate parallel flow pathway in the nutritive peripheral microcirculation, resulting in a reduction in the flow resistance and thereby a reduction in blood pressure required to circulate blood through the vascular system. Hermida et al. have documented conclusively that an overnight dip in blood pressure reduces the 5-yr probability by more than 40% of experiencing a blood vessel and organ pathology or a morbid and mortal cardiovascular disease event [53]. Thus, convective heat transfer via blood circulation from the core to glabrous skin plays an important role in the maintenance of health and well-being.

Spinal Thermoaffector Inputs to Regulate Blood Flow to Heat Exchanger Vessels in Glabrous Skin. The distribution of blood flow among various components of the peripheral vasculature is a dynamic and exceptionally complex process that requires an equally sophisticated control system with a multitude of parallel affecters and effectors [54]. The peripheral microvasculature in the skin can be viewed as consisting of two components having distinctly different control and heat transfer properties. Blood flow may be categorized as flowing to either glabrous or nonglabrous skin. In nonglabrous skin, the most peripheral vascular elements are capillaries that have a prime nutritional function. Alternatively, in glabrous skin, capillaries exist to service the nutritional needs of the tissue, but the AVAs also exist as short-circuit vessels between and arteriolar and venular networks. Blood flow to these different vessels plays a central role in thermoregulation [55], albeit with distinctly differing operational schemes. Taylor has provided a comprehensive and informative summary of the roles of the capillaries and AVAs in thermoregulatory heat transfer at the skin surface as a convective portal to the body core [25], and readers are directed to it for details that far exceed what can be covered in this paper. Some critical features can be noted briefly herein.

One major distinction between AVAs and capillaries is the flow diameters when they are fully vasodilated. Capillary diameters are in the range of 8–10 μm, while AVA falls between 10 and 150 μm [28], meaning that the AVAs have the capacity to support a much larger local blood flow rate and consequently, convective heat transfer. Thus, a prime physiological purpose of the AVA is to facilitate heat transfer, particularly so for executing convective heat flow between the core and the surface. Some data cited by Taylor make this point in a compelling manner [25].

Under hyperthermic stress, combined cutaneous blood flow to glabrous and nonglabrous skin can reach the range of 7–8 L/min. In combination with only a 1 °C differential in temperature between core and skin, the result will be a convective heat flow of 27 kJ/min which is equivalent to 450 W. However, it is important to realize that this blood flow is not evenly distributed over the entire body. Under conditions of vasodilation, the glabrous skin can accommodate blood flow rates that are more than threefold greater than the maximum in nonglabrous skin, with direct implications for supporting convective heat transfer in conjunction with thermoregulation of body core temperature. The rate of blood flow through glabrous skin can vary by orders of magnitude between minimum and maximum levels as functions of core temperature and of the average and local skin temperatures [25,56]. Peak flow rates go to more than 20 ml/(ml min). Body positioning also plays a role in that the foot perfusion rates can be significantly larger for a subject in the supine position as compared with standing, wherein the soft tissue of the sole is supporting body weight in the gravity field which produces a mechanical stress that opposes the blood perfusion pressure.

Control of skin blood flow is most commonly attributed to a combination of core and skin temperatures, with weighting toward the core [56,57]. Of particular interest to thermoregulation is blood flow to the glabrous skin that provides a primary route of convective heat flow between the body core and its environment. In particular, the hands and feet are prominent sites for GSBF, and additionally they have large values of surface area to volume ratio that facilitates heat interchange with the environment [25]. Effectively, they function as fins to increase heat transfer efficiency in addition to having large internal convective transfer.

The rate of blood flow to AVAs in glabrous skin is regulated by a complex closed-loop feedback system. Afferent inputs are generated centrally, locally, and peripherally (in a broadly integrated sense) [56]. Although primary input sensors are thermal, other types of sources may also be involved. For example, for some individuals, emotional stimuli can cause a rapid and major vasodilation of AVAs in the face and ears resulting in a reddening appearance (blushing) and warm sensation associated with a dense perfusion of blood from the core.

Normal vasomotive control of the AVAs is among the most dynamic of the entire peripheral vascular system, allowing for rapid major adjustments to accommodate changing needs for conservation or dispersal of body heat to match environmental conditions and/or the rate of internal metabolic generation [54]. Nonglabrous vasomotion is mediated by the combined action of active vasoconstriction and active vasodilation [58]. In stark contrast, vasomotion in AVAs is affected only by activation and relaxation of sympathetic vasoconstriction inputs [59,60]. Thus, AVA vasodilation results from the withdrawal of vasoconstriction and occurs passively in response to the systolic pressure provided by the heart. Also, the pattern of vasomotion in AVAs is strongly distinguished from that in the nutritive microvasculature, with a larger magnitude and frequency of oscillation [61,62].

It has long been recognized that the prime site for control of thermoregulation and therefore GSBF lies centrally in the preoptic anterior hypothalamus [63,64]. However, it is far less widely acknowledged that parallel peripheral extrahypothalamic control tissue exists, in particular, along the spinal cord [65,66]. This peripheral thermoregulatory control tissue may be accessed thermally to exercise control of thermoregulatory function and thereby to manipulate the body core temperature. We have devised methods and devices to execute thermal access to the control tissue lying along the spine and have termed the process selective thermal stimulation (STS) [30].

The high level of thermal functionality of the AVA network in glabrous skin enables it to be viewed as a physiological heat exchanger [67]. The properties and performance of glabrous skin, its embedded plexus of AVAs, and their range and mechanism of control align remarkably well with the features of devices that are known as compact heat exchangers in engineering parlance [68]. The flow of blood to the AVAs is modulated via an autonomous feedback control to adjust the heat exchange capacity to match the requirements of the immediate physiological state. The result is an elegant heat exchange system having a remarkable range of performance from near zero (under conditions of core energy conservation) to 200 W/m^2 by nonevaporative transport means for a resting individual in a thermoneutral air environment at 27 °C [25]. When phase-change heat transfer by sweating is added or water is substituted for air in the environment, the flux accommodated by glabrous skin heat transfer will be enhanced significantly.

Selective thermal stimulation provides a mechanism to directly intervene in the control of blood flow to the AVA heat exchange vessels in glabrous skin. Although it may seem counterintuitive to be able to influence blood flow in peripherally located elements of the circulatory system in the hands and feet by manipulating temperatures along the spinal cord, this approach is precisely matched with the functioning of the thermoregulatory system controller. Although this technology is novel in its application in humans, it has been documented widely since the 1930s [69–71] in numerous other mammalian and avian species. These include the ox, goat, sheep, dog, pig, cat, rat, monkey, guinea pig, pigeon, penguin, chicken, and rabbit. See Ref. [30] for dozens of specific references that are not integral to this publication.

The typical experimental techniques consisted for implanting a flexible polyethylene tube into the vertebral canal extending from

a cervical access port to the lumbar region and then looping back through which thermally conditioned water could be circulated from an external source [72]. In most cases, the tubing was left in place chronically so that serial trials could be conducted on the same subject. Thereby, the temperature of the spine could be altered locally independently of the core and preoptic anterior hypothalamus temperatures. In some cases, a separate water circulation loop was implanted around the hypothalamus to manipulate its temperature independently. Truly remarkable results were achieved in which animals were placed in oppressively hot environments, and cold water was circulated through the tubing causing the animals to constrict AVAs and to shiver to generate excess internal heat generation, which is the exact opposite of a normal thermoregulatory response. The inverse effect was also demonstrated with animals in a cold environment, while hot water was circulated through the tubing resulting in AVA vasodilation to facilitate heat rejection. The physiological responses were proportional to the STS temperature, indicating a dose dependent behavior. The time constant for thermoregulatory response to invoking a differential temperature along the spinal cord was on the order of 10 s [73]. Thus, the spinal cord provides an effective site to access the thermoregulatory control system to manipulate its function.

The ability to intervene into thermoregulatory function can have important benefits in humans for therapeutic, prophylactic, and comfort objectives. Obviously, such invasive means as implanting a water circulation tube into the vertebral canal cannot be applied for humans. However, surface heating is an alternative, while exercising caution to avoid temperatures hot enough to cause a thermal injury—43 °C [74]. We have also used penetrating heat, such as an infrared source, to more effectively transfer heat to the site of thermal control sensors. However, such approaches require exercising great caution to avoid causing thermal damage to the spinal cord, which could have severe consequences.

We [30] and many other researchers (summary by Taylor [25,30]) have observed that there is a memory effect associated with the recovery of elevated perfusion status from depressed blood flow, especially from a state of hypothermic-induced vasoconstriction, when the surface boundary conditions (skin temperature) are returned to normothermia inducing conditions. We have termed this effect as thermoregulatory inertia, based on time constants associated with internal and external heat transfer processes [30]. The implication is that it requires time to coax GSBF to be altered to a new level, especially when it has been vasoconstricted. Another factor contributing to this behavior is the unique control mechanism of AVA vasomotion that occurs only via sympathetically induced vasoconstriction in contrast to the nonglabrous vasculature that responds actively to both sympathetic invoked vasoconstriction and vasodilation. AVAs vasodilate only by passive elastic response to internal perfusion pressure from blood offsetting the level of active vasoconstriction as the sympathetic control input is progressively withdrawn.

Another arena of bioheat transfer in which control of AVA blood flow plays a major role occurs during the time when patients are anesthetized during surgery. Many anesthetic agents exist, nearly all having the common consequences of effectively paralyzing the thermoregulatory control apparatus. Therefore, sympathetic vasoconstriction ceases to exist, and the AVAs vasodilate under the pumping pressure of the heart, elevating blood flow to glabrous skin. The result is that a major convective heat leak is formed between the body core and the surface, sometimes causing a precipitous drop in core temperature. This phenomenon is particularly troublesome for individuals in the operating room where the typical air temperature is on the order of 20–22 °C and the palms and soles are often exposed directly to the air. Given the large temperature differential between blood circulating through the AVAs and the environment air, about 15 °C, there is a resulting loss of heat from the core that will issue in a state of hypothermia for an anesthetized patient. A drop of even 1 °C in the core body temperature can lead to compromise in the blood clotting process and immunological suppression [75,76]. Therefore, active patient warming is mandated in most surgical environments. Multiple styles of devices have been developed for this purpose that perform with varied levels of thermal efficacy, each having unique advantages and disadvantages.

Although water circulation and electrical resistance heating pads are available [77,78], the most widely applied method is forced air warming (FAW) in which the patient is covered with a porous blanket that has internal circulating heated air [79,80]. The device is simple to use, and it is claimed that up to 80 W of heating can be added to the body surface via FAW when large areas of the skin surface are heated. This method depends serially on convection from air to the skin surface, conduction through the nonglabrous skin and convection with blood flowing through the microcirculation, and finally convective flow as blood returns to the core. The microcirculation in nonglabrous skin is evolved primarily for nutritional and fighting infection, plus contributing to thermoregulation. However, geometry and velocities compromise its effectiveness in forced convection heat transfer in comparison to the much larger AVAs. Therefore, based on the inherent properties of its design, FAW targets a low performance area of the body surface for heat transfer and must depend on recruiting large areas to compensate. FAW blankets often occupy large, or even major, areas of the body surface, impeding access for some surgical procedures. In many configurations, exhausted air from a warming blanket is directed in a downward pattern where it may pass across the floor beneath a surgical table and have the opportunity to entrain dirt bacteria. Eventually, the warm air rises under buoyant action and may pass by the surgical field and instrument trays with the possibility of introducing infectious agents. There have been hundreds of reported infections by microbes typically found on floors, particularly in conjunction with joint implants, that have been attributed without explicit proof to transmission by FAW exhaust flow [81,82]. No mechanistic causative studies have been conducted on human subjects to establish whether there is a direct coupling effect between the convective flow of FAW exhaust gas and surgical site infections. A definitive study of this phenomenon is not likely to be approved owing to the unacceptable danger to subjects. Further, air is a relatively poor convective heat transfer fluid in comparison with liquid medium options. Water is considered the most useful liquid for medical applications. However, controlling flow patterns and spill remediation is much more problematic with a liquid than with air. Clearly, there remain opportunities for innovation contributions from the heat transfer community in perioperative warming. Of course, all new devices must pass review by the FDA be at a competitive price point and be perceived as advantageous within the medical community.

Applications of Targeted Selective Heat Transfer for Manipulation of Thermoregulatory Function

The ability of STS to access control of AVA blood flow that is a prime component of thermoregulatory function opens unique opportunities to develop and apply new technologies having immense potential medical impact. STS is a new technology when applied to humans, and it is yet to be refined into approved medical devices. Nonetheless, there are numerous diverse possibilities that have been identified and that are described in the following brief commentary. A compilation of exemplar medical applications for core temperature manipulations is given in Table 1.

Sleep Onset Enhancement. An important application of STS involves enhancing the onset and quality of sleep. The human thermoregulatory system operates on a circadian cycle in coordination with sleep [83,84]. The thermoregulatory cycle is functionally involved in driving the sleep-onset process [85], although the

Table 1 Some examples of medical applications of technologies to manipulate thermoregulatory function

Technology	Applications
Therapeutic hypothermia	Traumatic brain injury therapy
	Major organ failure
Perioperative warming	Maintaining normothermia during anesthesia
Selective thermal stimulation	Sleep induction
	Thermal comfort
	Regulation of blood pressure

inverse is not true [86], plus GSBF plays a key role in governing sleep performance. Kräuchi and colleagues [45,87] have shown that modulation of blood flow to AVAs in glabrous skin of the hands and feet is integral to determining sleep quality. Vasodilated AVAs (warm hands and feet) promote rapid sleep onset [87], whereas vasoconstricted AVAs produce delayed sleep onset [45]. In the present context, it is of note that STS can be used to modulate GSBF.

Physiological sleep data show that as late hours in the circadian cycle approach, there is a significant upregulation in GSBF, opening the primary heat exchange portal from the warmer core to the (usually) cooler environment. A subsequent drop in core temperature occurs via enhanced convection of blood to glabrous skin, facilitating the loss of core heat to the environment, with a time constant on the order of 2–3 h, and with sleep onset following thereafter in an additional 0.5 h [88]. Absence of the normal nocturnal decline in core temperature by approximately 1 °C can be associated with sleep-onset insomnia [89]. Common causes of abnormally high nighttime temperature are improper indoor air circulation, circadian rhythm dysregulation (e.g., jet lag, shift work), and thermoregulatory dysfunction. The latter condition may occur at any time of year and is thought to affect tens of millions of Americans. Typical accommodation is attempted by downward adjustment of the air temperature in the bedroom, with targets as low as 60 °F to 68 °F (15.6 °C to 20 °C), often to the discomfort and consternation of a sleeping partner.

Another important benefit of AVA vasodilation during sleep is that the diminished terminal vascular resistance to blood flow results in a reduced sleep-time blood pressure that is increasingly recognized as protective against risk of cardiovascular diseases and major organ (kidney, eye, etc.) pathology [41,90]. An overnight dip in blood pressure has been identified as a significant contributing factor in lowering the occurrence of cardiovascular-derived events by as much as 40% or more, even when daytime blood pressure is elevated (hypertensive) [91].

Selective thermal stimulation may be efficacious for enhancing sleep onset and quality and for facilitating a transient drop in overnight blood pressure by suppressing vasoconstriction of AVA flow. STS may be applied immediately prior to the desired time of sleep onset to cause a defined set of physiological responses: distal AVAs will be vasodilated, resulting in warming of hands and feet; core heat loss via GSBF will increase, precipitating an early initiation to the desired overnight core temperature drop; and the beneficial dip in blood pressure will begin early in the sleep cycle, providing an extended period of overnight cardiovascular recovery.

Figure 3 shows overnight physiological data for a sleeper with and without the application of STS for a brief period at bedtime. These data illustrate the efficacy of STS relating to sleep function for a subject who typically experiences difficulty falling asleep after going to bed and entering a productive sleep state. The data start with a 20-min baseline data-acquisition period prior to STS. Figure 3(*a*) illustrates blood flow to glabrous skin on the sole of the foot, as monitored with a laser Doppler flowmeter. In the control trial without STS, the blood flow is in continuous decline for more than 3 h, which is associated with difficulties in sleep onset. With STS applied, blood flow to the feet is initiated early in the sleep cycle and rises rapidly to a maximum value that is maintained through the night. Figure 3(*b*) presents data for surface temperature on the sole of the foot. Both the control and STS trials directly reflect the levels of GSBF. Warm feet are consistent with a period required for sleep onset that is threefold shorter on

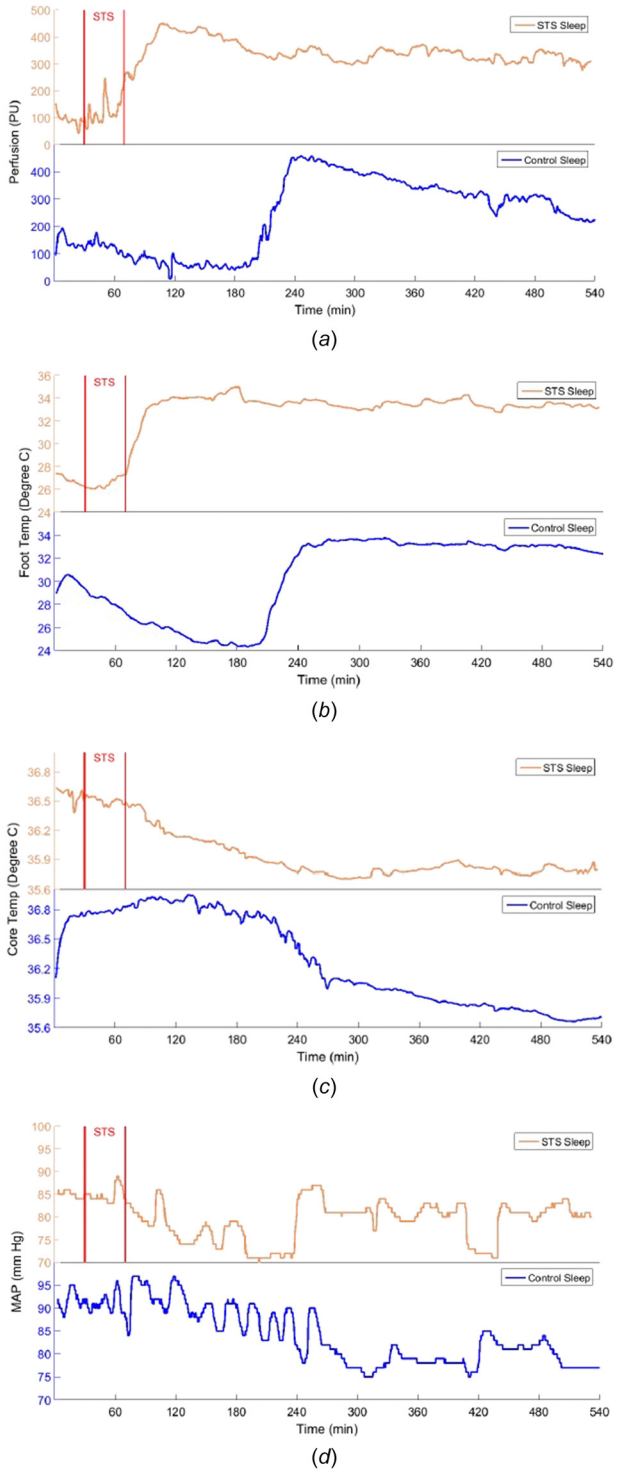


Fig. 3 Overnight physiological data measured on a subject who slept one night without using STS (*lower blue plots*) and one night with STS applied for 30 min at bedtime (*upper orange plots*). The start and finish of STS are denoted by the vertical lines. (*a*) Blood flow to glabrous skin of the foot measured from an initial 20-min baseline period. (*b*) Temperature on the foot sole. (*c*) Core temperature measured with a sublingual probe. (*d*) MAP. Adapted from Ref. [92].

average [87]. Low blood flow results in a sensation of cold feet. Figure 3(*c*) shows overnight core temperature values. A significant decrease in core temperature is required for a high-quality sleep experience [51,83,93], and heat transfer from glabrous skin with a high blood-perfusion rate is the key to eliminating heat from the body core. With the upregulation in GSBF produced by STS, core body temperature drops immediately and continuously to the overnight nadir. In contrast, for the control trial, core body temperature remained highly elevated for several hours before an eventual drop. The time lag of nearly 4 h probably represents a loss in restorative sleep potential through the night. Figure 3(*d*) shows the continuously monitored mean arterial pressure (MAP). Longitudinal studies have documented long-term health benefits from an extended significant dip in MAP during sleep [90]. With early STS-induced vasodilation of large-bore AVAs (approximately ten times the diameter of capillaries), the cardiovascular resistance against which the heart must pump is reduced, thereby allowing the system to depressurize overnight. In contrast, in the absence of STS at the start of the overnight cycle, the MAP remains elevated for hours before eventually dropping.

Implementation of STS in the sleep environment can be minimally obtrusive and may be a valuable technology to increase sleep performance and to mediate blood pressure to benefit overall health and well-being. For people who suffer from insomnia associated with thermoregulatory dysfunction, STS can provide a direct method for relief. For people who are "normal" sleepers, STS is still likely to lead to an improved sleep experience and daytime function, especially in those who experience cold feet at bedtime.

Perioperative Warming. The objective of perioperative warming of anesthetized patients is to block the procession of their becoming hypothermic by more than 1 °C. As noted earlier, well established means are available to provide warming to anesthetized patients, most commonly by FAW. However, elements of this technology are less than optimal from a thermal design perspective in addition to not being well matched to native physiological function. Our research team has conceived of and devised a new technology designed to take advantage of the inherent physiological basis of thermoregulatory functions. Accordingly, the perioperative warming technology is called WarmSmart, since it recruits and enhances the existing heat flow pathways between the core and skin simultaneously to block the major loss mechanism of heat during anesthesia and to add heat to the core to avoid the occurrence of hypothermia.

We have demonstrated that STS application can delay the onset of AVA vasoconstriction during body cooling [94]. Experiments were conducted with subjects wearing full body (to the wrists, ankles, and neck) water perfusion garments to enable independent control of skin temperature. Laser Doppler probes were applied to glabrous and nonglabrous skin to monitor skin blood flow. Mean skin temperatures were monitored with two-dimensional resistance temperature detectors fabricated by knitted insulated copper motor winding wire [95], affixed to the thigh, chest, triceps, and along the spine at the STS heating site. Core temperature was monitored via an ingestible thermistor embodied in a pill pod with a transmitter to broadcast the temperature to an external receiver.

The trial protocol consisted of an initial passive baseline period followed by lowering the suit water temperature to the point where there was no further vasoconstriction for the subject on that particular day. Next, the suit water temperature was adjusted to 40 °C and held for 30 min to allow subjects to reach their personal maximum level of vasodilation on the trial day. If the experiment included STS, after the initial 15 min of warming a resistance heater was set to hold a temperature of 40 °C on the skin surface overlying the cervical region of the spine. The STS heater remained energized for the duration of the experiment. Following 30 total minutes of warming, water bath temperature was decreased at 1 °C/min until a state of maximum vasoconstriction was observed for 5 min. Each of our subjects underwent control and STS trials separated by at least 7 days. The hypothesis was the application of STS would result in a lowering of the mean skin temperature that caused a reduction in GSBF, thereby facilitating convective transport of energy between the skin and the core to a lower core thermal state to aid in defending against the onset of perioperative hypothermia.

Aggregate data from control and STS trials on four subjects are shown in Fig. 4. The order of STS and control was randomized. For each subject, when STS was applied, GSBF was maintained at a higher level to lower mean skin temperatures. The temperature differential between control and STS perfusion was minimal, near zero, for the highest perfusion rates, i.e., under conditions of maximum vasodilation for which sympathetic vasoconstriction was under greatest suppression associated with an elevated mean skin temperature. As the mean skin temperature was reduced, the efficacy of STS in suppressing AVA vasoconstriction progressively increased. For the four subjects, blood flow was maintained to the AVAs to lower temperatures of approximately 2, 2, 3, and 4 °C. Thus, with STS applied, heat can be convectively delivered to the body core at lower temperatures, reducing thermal isolation and defending against the onset of hypothermia.

In every case, GSBF was maintained to a lower mean skin temperature with the implication that STS will enable heat to be transported to the core under conditions for which it would otherwise not be possible, thereby contributing to the avoidance of perioperative hypothermia.

Therapeutic Hypothermia. The same physiological and device principles that are the foundation of WarmSmart for providing effective perioperative warming can also be applied to cool the body core under conditions for which therapeutic hypothermia (TH) would be of medical advantage. In this context, it is desirable to effectively be able to withdraw heat from the core to produce a lower temperature under conditions for which there has been a major internal organ trauma, resulting in a reduction in injury processes that are rate dependent on tissue temperature. TH has been practiced in a limited context for many years, but is limited in part by the body's built-in mechanism to guard the core against cooling below the normal circadian range. It is thought that a reduction as small as 1 °C can be of advantage, and reductions in the range of 3–4 °C are often sought. TH is frequently induced in a medical facility using water circulation cooling pads

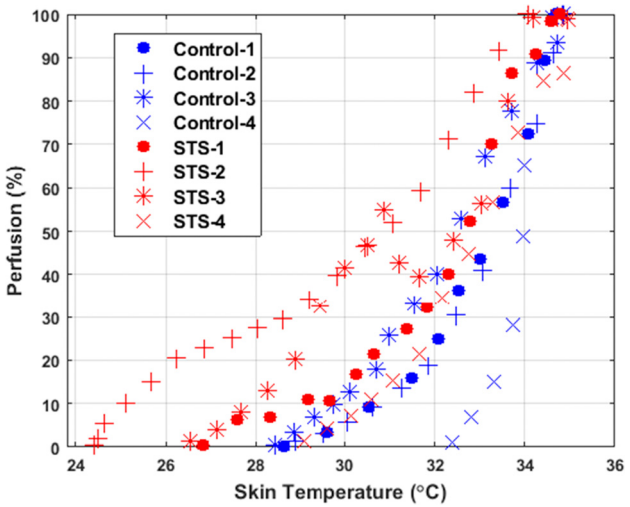


Fig. 4 GSBF plotted as a function of mean skin temperature during active vasoconstriction. The 0% and 100% perfusion represent the minimum and maximum values for that subject on the trial day. Each subject has the same symbol for their control and STS data (currently unpublished data).

applied over much of the body surface. The result is massive cutaneous vasoconstriction, meaning the heat withdrawal from the core occurs primarily via conduction through serial layers of tissue, such as bone, fat, muscle, and skin, that do not have an advantageous thermal conductivity. Consequently, TH induction is a slow process requiring hours. Unfortunately, it has become clear that the more rapidly TH can be established following a traumatic event, the better is the outcome for the patient. Ideally, TH can be initiated in the field, but the apparatus used in medical facilities is not compatible with remote application. Various means have been attempted to solve this problem, but there does not exist an accepted solution. Enter another opportunity for innovations by heat transfer engineering.

A thermal complement to WarmSmart has been developed called SmartCool. In the same principle, elevated heat flow is established between the core and the skin by application of STS to cause vasodilation of the AVAs which increases the blood flow. In the case of SmartCool, the objective is to remove heat from the core, which the body resists when the temperature drops below the thermoneutral state. The principal mechanism of thermal protection of the core is to vasoconstrict blood flow to the AVAs, which is why most people are familiar with the initial response to cold exposure is a sensation that the hands and feet are also becoming cold (due to lack of blood perfusion through the AVAs). As AVA perfusion is reduced by the body's natural defense response, the capacity for a convective heat flow from the core necessary to initiate TH is lost.

The potential of STS in to elevate blood flow to the primary cutaneous heat exchange vessels in glabrous during anesthesia was confirmed in a pilot study with 12 patients of diverse ages and medical conditions undergoing various types of surgery under full anesthesia. Anesthesia is generally considered to block sympathetic vasoconstriction of the AVAs, resulting in a high level of GSBF. For this set of trials, STS was applied 1 h after induction of anesthesia, and GSBF was monitored by plethysmography. Although there was considerable variation in response among the heterogeneous population of subjects, there was on the average about a 40% upregulation in GSBF following STS application, even though anesthesia-induced vasodilation of AVAs was already in effect. The implication is that a relatively small targeted application of heating to strategic thermal control tissue can be leveraged to manipulate a massive blood flow between the surface and core that has the potential to move large amounts of heat into and out of the body. Similar results have been achieved in prior experiments on many mammalian species [30].

Concluding Thoughts

Bioheat transfer plays an integral role in human thermoregulation. Recent advances in bioheat transfer research have identified selective thermal stimulation by applying small doses of heating to key control tissues readily accessible from the skin surface to manipulate thermoregulatory function by upregulating the convective delivery of heat by blood flow between the body core and surface. In principle, a small magnitude of STS energy input can be amplified into a large thermoregulatory energy response by the body core. This technology can be applied to design and implement thermoregulation manipulation intervention devices for therapeutic, prophylactic, and thermal comfort applications. Accordingly, there remains a major opportunity to apply engineering heat transfer principles to further develop and exploit this technology for medical and commercial benefit.

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Dedication

This paper has been prepared to honor the memory and legacy of Professor Ernest G. Cravalho, a career faculty member in the Mechanical Engineering Department at M.I.T. and the doctoral supervisor of the senior author (K.R.D.). Professor Cravalho was a true visionary pioneer in the field of bioheat transfer who contributed in key dimensions to development of the nascent science in this discipline and more generally to the establishment of biomedical engineering as a new and exciting arena of research and study. Further, in his role as professor and mentor, he had an inspiring, guiding influence on many students who have gone on to become national and international leaders in biomedical engineering. The impact of this life and work will last and be appreciated for many years to come.

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